THE STORY OF YELLOW FEVER SINCE WALTER REED*

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YELLOW fever was a scourge of mankind at the close of the last century. Not only was there a threat of occurrence of epidemics in the more staid, temperate-zone countries, but such epidemics did occur, and they were devastating. Global epidemiologists were well aware of the fact, still unexplained, that the teeming populations of the Orient had not been visited by the disease, and there was actually opposition in some circles to the construction of the Panama Canal, lest this new route result in the introduction of the dread disease to the Orient.

Epidemiology was a fast-moving field in 1900. The concept of vectors of disease was on a sound footing, following discoveries of Theobald Smith, Ronald Ross, Patrick Manson, and others. Attempts to establish the epidemiology of yellow fever on a direct person-to-person transfer basis had failed repeatedly. However, Carlos Finlay, a Trinidad-born Scot resident in Cuba, had proposed a novel theory to explain transmission (novel for 1881, and perhaps not so novel for 1900) and actually made attempts, using *Aedes aegypti*, to transmit the disease by mosquito bite. He did not include an incubation period in the mosquito as part of his procedure. Henry Carter Rose, studying the course of epidemics in the southern United States, postulated an incubation period of two to three weeks between one wave of infection and the next.

The direct involvement of the United States in affairs south of the border at the close of the last century focused attention on the problem of yellow fever. The contributions of the United States, through army investigators and later through the program supported by the International Health Division of the Rockefeller Foundation, toward the resolution of the problem constitute one of the most distinguished chapters in the history of the conquest of disease. Not only was major progress

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made toward the domination (if not the total conquest) of yellow fever, but many of the contributions were in the mainstream of development of general concepts of the virus moiety itself, or virus vectors, virus epidemiology, and virus vaccines.

The history opens with the contributions of the members of the United States Army Yellow Fever Commission, formed in 1900, headed by Walter Reed and including James Carroll, Jesse W. Lazear, and Aristides Agramonte. Volunteers from the ranks (the list of names can be found in Scott's *History of Tropical Medicine*) permitted themselves to be used as test subjects to explore possible mechanisms of infection.

The stage was set, the time was ripe, and within a year proof was at hand that yellow fever could be transmitted by *A. aegypti* following an incubation period of about 12 days in the mosquito, could be transmitted by inoculation of blood from an infected person in the first or second day of illness, and was not conveyed by fomites. Reed and Carroll further demonstrated that the causative agent was filtrable, in their own words "an organism so minute in size that it might be designated as ultramicroscopic."

When Wilbur Sawyer of the Rockefeller Foundation was conducting a worldwide survey of yellow fever immunity based on a virus-neutralization test in mice, John Kissinger, one of the volunteers from the Havana experiments was located and a sample of his serum was obtained. This sample neutralized yellow fever virus—additional confirmation, if such were needed, of the brilliant experiments carried out by the Yellow Fever Commission.

These discoveries were followed shortly by the dramatic demonstration, engineered by William Crawford Gorgas, of yellow fever control. By September 1901, yellow fever had been completely eradicated from Havana by a program of antimosquito measures directed against *Aedes aegypti.* This demonstration was repeated in Panama by Gorgas and in Rio de Janeiro by Oswaldo Cruz.

Measures to control *A. aegypti* were instituted in most tropical ports of the new world, and one may surely conclude that, even though the mosquito remains, the earlier conditions of uncontrolled, exuberant infestation, providing a most fecund seedbed for amplifying epidemics, will probably never be seen again. Even the 100 per cent rates of infestation for *A. aegypti* occasionally seen in domiciliary checks today do not mean that numbers of the mosquito are great; they usually are not. Peo-

ple today probably do not tolerate as many mosquitoes as they did a generation or two ago.

Fears, particularly in the Far East, that the opening of the Panama Canal might expose that part of the world to the introduction of yellow fever contributed to the pressures which resulted, in 1916, in the formation of the Rockefeller Foundation Yellow Fever Commission, with General Gorgas, Henry Rose Carter, Juan Guiteras, T. C. Lyster, E. R. Whitmore, and W. D. Wrightson as members. The early efforts of this commission were successful in eradicating yellow fever from Guayaquil, and its efforts were extended to many other Latin American countries.

Meantime Hideyo Noguchi of the Rockefeller Institute, in work supported by the Rockefeller Foundation, advanced his claim that the causative agent of yellow fever was *Leptospira icteroides*, a claim not completely squelched for nearly a decade.

In the mid-1920's additional commissions supported by the Rockefeller Foundation went to West Africa, assessed the problem, and recommended the establishment of permanent quarters for a West Africa Yellow Fever Commission in Yaba, near Lagos, Nigeria. Henry Beeuwkes headed this commission. Significant findings followed in rapid succession. Mahaffy and Bauer designated the rhesus monkey as a suitable laboratory animal. Stokes, Bauer, and Hudson in 1927 confirmed definitively that the yellow fever agent was a filtrable virus, and also established that the disease could be transmitted from monkey to monkey by inoculation of blood, and from monkey to monkey by *A. aegypti* mosquitoes. They also showed that mosquitoes, once infected, remained infective for the entire period of their lives, and that a single infected mosquito could induce infection by bite.

Johannes Bauer, and later Cornelius Philip, showed that yellow fever could be transmitted by mosquitoes other than *A. aegypti*. These observations were extended by Nelson Davis and Raymond Shannon, staff workers of the Rockefeller Foundation, in Brazil, in work with a Brazilian mosquito, *Aedes scapularis*.

In 1928 the Rockefeller Foundation Yellow Fever Laboratory, under the International Health Division of the Rockefeller Foundation, was established in quarters provided by the Rockefeller Institute for Medical Research in New York City. Wilbur A. Sawyer was the first director. An early statement of his can be used to summarize the danger and the drama of this period. Sawyer wrote: "The recent tragic deaths of

Stokes, Noguchi, and Young were fresh in mind and had shown how great a risk was run in yellow fever research even by the most skilled of laboratory workers. It was accordingly decided, for safety, that only medical men should be allowed to participate in the work during the early stages. With full realization of the danger, Dr. Wray Lloyd and Dr. S. F. Kitchen, both of the University of Western Ontario, agreed to take part. Together we carried out the experiments, fed the monkeys, took their temperatures, cleaned and sterilized their cages, performed the necropsies when they died, and incinerated the bodies and rubbish. All through the hot summer months we labored thus in mosquito-proof rooms with screened vestibules. In October, Dr. Martin Frobisher, Jr., formerly instructor in the Johns Hopkins Medical School, joined the staff, and it was decided that it would be permissible to employ mature assistants to help with the animals, and do technical work if they were fully informed of the danger they would run. In most cases, the blacker we painted the picture, the more eager were the applicants to take the positions."

Max Theiler, working at Harvard, in 1930 reported on the use of the white mouse, inoculated intracerebrally, for studying the virus, and described modification or "fixation" of the virus by passage through mice. Shortly thereafter he described a mouse-protection test. The mouse-adapted virus was first used to protect laboratory workers in a vaccine mixture consisting of 10 per cent suspension of infected mouse brain tissue in human immune serum. This and later vaccines ended the tragic succession of death and illness in laboratory workers.

The mouse-protection test developed by Sawyer and Lloyd permitted a worldwide survey for yellow fever immunity. The test employed, with intraperitoneal inoculation of virus-serum mixtures into adult mice, combined with intracerebral inoculation of a starch suspension, was relatively insensitive. In consequence, an amazingly accurate picture of disease distribution was obtained. Had the refinements which increase the sensitivity of the test been known and used at that time, and had later techniques of complement fixation, hemagglutination inhibition, and tissue-culture neutralization been available, the investigators of 35 years ago would have encountered the bewildering complexity of the Group B arboviruses, relatives of yellow fever, and the clear-cut definition of yellow fever distribution would have been obscured. The serological patterns produced with use of the more mod-

ern techniques are much less easy to interpret than the old crude pattern, and today, when one requires a specific "yes or no" reply to the still important question of "yellow fever or not yellow fever" one falls back on an adult mouse virus-neutralization test for the answer.

Theiler's mouse-adapted yellow fever virus was further passaged by French workers, and the French neurotropic strain of vaccine virus was developed at Dakar and subsequently used extensively in vaccination programs, principally in French Africa. This mouse-brain vaccine gives excellent protection against yellow fever but is attended by a disturbingly high rate of serious reactions, especially in children.

Theiler and Hugh Smith, working in the Rockefeller Foundation Yellow Fever Laboratory in New York, succeeded in culturing an African strain of yellow fever virus, the Asibi strain, in chick embryo tissue cultures (well before the advent of the antibiotic era); this included a final series of passages in embryo from which the brain and spinal cord components had been removed before mincing. The 17D strain of virus was identified as having both the viscerotropic and neurotropic virulence of the virus markedly reduced, and this strain has served as a model vaccine, the best virus vaccine yet developed. Large-scale immunizations were first begun in 1937. In the succeeding 30 years no case of yellow fever has been identified in a person who had received inoculation of viable vaccine at any time in his life. The time interval is still too short for certainty, but the conclusion is that life-time immunity is conferred by a single inoculation of viable 17D virus. An error in judgment led to the inclusion of human serum in the vaccine lots prepared for large-scale immunization and, as a result, many cases of serum hepatitis, with many deaths, occurred in vaccinated American servicemen in the early months of World War II. Human serum was excluded from later batches of vaccine and no further trouble was experienced.

While the laboratory end of yellow fever investigations was proceeding thus favorably, the epidemiological picture, so brilliantly illumined by Reed and Gorgas, was being clouded. Control work directed at *A. aegypti* in urban centers cleared up the transmission of yellow fever in these centers. But evidence was accumulating in Colombia, and in Brazil particularly, about outbreaks where *A. aegypti* was not involved. Fred L. Soper in the mid-1930's defined a new epidemiological concept, jungle yellow fever, as "yellow fever occurring in rural,

jungle and fluvial zones in the absence of *A. aegypti.*"

Laboratories supported by the Rockefeller Foundation in Rio de Janeiro, Bogotá, Entebbe, and Lagos addressed themselves to the problem of jungle yellow fever. Raymond Shannon, Loring Whitman, and Mario Franca in 1938 demonstrated transmission of yellow fever with a naturally infected, wild-caught *Haemagogus spegazzinii*, and Jorge Boshell in Colombia made the important observation that *Haemagogus* mosquitoes spent their winged lives by preference in the forest canopy. Richard M. Taylor, Hugo Laemmert, and José Fonseca da Cunha participated in studies in the region of Ilhéus, Brazil, further confirming the monkey-*Haemagogus*-monkey cycle.

Similar studies were conducted in Bogotá, with John Bugher, Marston Bates, John Weir, and Charles Anderson involved, along with several Colombian collaborators, among them Hernando Groot, Augusto Gast Galvis, and Jorge Boshell. In this same period Alexander Mahaffy, Kenneth Smithburn, Alexander Haddow, George Dick, and others were busy unraveling the story of yellow fever in East Africa, and they succeeded in outlining an epidemiological pattern of yellow fever spread there. This outline had certain features in common with the South American story, and certain pronounced differences.

The verification of the concept of jungle yellow fever put an end to the dreams of eradicating yellow fever. However, there was and is no cause for general alarm. An effective vaccine exists, and any person or group of people desiring protection can be protected. Nevertheless, a gap still exists between the desired and the attainable end. In the short period since 1950 there have been serious outbreaks of yellow fever in Central America, Trinidad, Argentina, Ethiopia, Senegal, and Portuguese Guinea, and sporadic cases have been reported from several other countries. The toll of deaths in these outbreaks is many thousand; the largest contribution to this total was that of the extensive outbreak in 1962 in Ethiopia.

A further threat to international public health exists with the possibility, which is greater every day, of transporting an infector vector or infected human from an affected to an unaffected region.

To pick up the story of yellow fever control, by control of *A. aegypti* since Gorgas, a signal triumph was achieved when *A. aegypti* was eradicated from Brazil; this was the culmination of a venture backed by the Rockefeller Foundation; it included the participation

of many American workers: Fred Soper, Austin Kerr, Bruce Wilson, Raymond Shannon, Nelson Davis, Loring Whitman, Edwin Lennette, and others. Serious efforts have been made by local governments and the Pan American Health Organization to eradicate *A. aegypti* from the Western Hemisphere. The United States Public Health Service has recently joined this effort, in an attempt to eradicate the mosquito from the United States. The story of the eradication of *A. aegypti* can be condensed into three epochs. First is the era before DDT and other insecticides, when a program such as the Brazilian one was achieved through a marvelous machinery of check and cross-check, coupled with excellent field strategy and dogged persistence. Second is the DDT era, when success followed success with very much less effort than that expended in the earlier period. Finally there is the unhappy present, in which the insecticide-resistant *A. aegypti* are widespread, in which epidemics transmitted by *A. aegypti* occur, as witness the recent dengue epidemic in the West Indies and northern South America, and there have been reports of reinvasion of formerly clean territories, including Guyana, Trinidad and Belém, Brazil.

It would appear that the work of eradicating *A. aegypti* will have to return to the first premises established by Gorgas and employed so brilliantly by Soper, and then shelved for a quarter of a century.

Investigations into yellow fever initiated by the U.S. Army and continued by the Rockefeller Foundation contributed many fundamental observations which enriched the fields of virology and epidemiology, and they continue to do so. An immediate outgrowth of the program is the current program on arboviruses, which is supplying a seemingly never-ending stream of challenging virus entities that demand continuing virological and epidemiological studies of a complexity undreamed of half a century ago, when the first and still the most important arbovirus, yellow fever, was making its scientific debut.

Few remain who personally knew any of the individuals involved in the early yellow fever story. And the names of those who died of the very disease they were working on fade from memory. In solemn recognition of the contributions of past workers, it is appropriate here to name those investigators who gave their lives, in full awareness of the risks involved, in the search for the truth about yellow fever: Adrian Stokes, Hideyo Noguchi, William Alexander Young, Theodore B. Hayne, Paul A. Lewis, Howard B. Cross, and Jesse Lazear.